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Syringocystadenoma Papilliferum of the Anogenital Area and Buttocks: A Report of 16 Cases, Including Human Papillomavirus Analysis and HRAS and BRAF V600 Mutation Studies

Konstantinova, Anastasia M ; Kyrpychova, Liubov ; Nemcova, Jana ; Sedivcova, Monica ; Bisceglia, Michele ; Kutzner, Heinz ; Zamecnik, Michal ; Sehnalkova, Eva ; Pavlovsky, Michal ; Zateckova, Kamila ; Shvernik, Sergej ; Spurkova, Zuzana ; Michal, Michal ; Kerl, Katrin ; Kazakov, Dmitry V

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Syringocystadenoma Papilliferum of the Anogenital Area and Buttocks: A Report of 16 Cases, Including Human Papillomavirus Analysis and *HRAS* and *BRAF V600* Mutation Studies

Anastasia M. Konstantinova, MD, PhD,†‡ Liubov Kyrpychova, MD,§ Jana Nemcova, MSc, PhD,§¶ Monica Sedivcova, MSc,¶ Michele Bisceglia, MD,‖ Heinz Kutzner, MD,** Michal Zamecnik, MD,†† Eva Sehnalkova, MD,‡‡ Michal Pavlovsky, MD,§§ Kamila Zateckova, MD,¶¶ Sergej Shvernik, MD,‖‖ Zuzana Spurkova, MD,‖‖ Michal Michal, MD,§¶ Katrin Kerl, MD,*** and Dmitry V. Kazakov, MD, PhD§¶****

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Abstract: Syringocystadenoma papilliferum (SCAP) is a benign tumor most commonly located on the head and neck area often associated with nevus sebaceus. In its usual location, the human papillomavirus (HPV) DNA and mutations in the RAS/mitogen-activated protein kinase signaling pathway have been detected in SCAP. We studied 16 cases of SCAP in the anogenital areas and buttock where this neoplasm is rare and attempted to find out whether SCAP in these sites have different histopathological and molecular biological features. It seems that there is no significant difference between the morphology of anogenital SCAP and SCAP in other locations. Several tumors in our cohort demonstrated features resembling those seen in warts, but HPV DNA was not found in these lesions. On the contrary, we identified DNA of HPV high-risk types in some tumors without HPV-related morphology. Our study confirms the role of *HRAS* and *BRAF V600* mutations in the pathogenesis of SCAP, including SCAP in the anogenital areas and buttock.

Key Words: adnexal tumors, syringocystadenoma papilliferum

From the *Department of Pathology, Clinical Research and Practical Center for Specialized Oncological Care, Saint-Petersburg, Russia; †Department of Pathology, Medical Faculty, Saint-Petersburg State University, Saint Petersburg, Russia; ‡Department of Pathology, Saint-Petersburg Medico-Social Institute, Saint Petersburg, Russia; §Sikl's Department of Pathology, Medical Faculty in Pilsen, Charles University in Prague, Pilsen, Czech Republic; ¶Bioptical Laboratory, Pilsen, Czech Republic; ‖Anatomic Pathology, School of Biomedical Sciences, Etromapmax Pole, Lesina (FG), Italy; **Dermatopathologische Gemeinschaftspraxis, Friedrichshafen, Germany; ††Agel Laboratory of Pathology, Novy Jicin, Czech Republic; ‡‡Department of Pathology, Silesian Hospital, Opava, Czech Republic; §§Department of Pathology, Regional Hospital Most, Czech Republic; ¶¶Department of Pathology, Regional Hospital Decin, Decin, Czech Republic; ‖‖Department of Pathology, Bulovlka Hospital, Prague, Czech Republic; and ***Department of Dermatology, University Hospital Zurich, Zurich, Switzerland.

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The authors declare no conflicts of interest.

Correspondence: Dmitry V. Kazakov, MD, PhD, Sikl's Department of Pathology, Charles University Medical Faculty Hospital, Alej Svobody 80, 304 60 Pilsen, Czech Republic (e-mail: kazakov@medima.cz).

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INTRODUCTION

Syringocystadenoma papilliferum (SCAP) is a rare benign adnexal neoplasm occurring either sporadically or as a secondary tumor in nevus sebaceus of Jadassohn. The commonest affected site is the head and neck area.[1] The trunk and extremities are occasionally involved, whereas lesions involving the groin, buttock, and anogenital SCAP have rarely been reported.[2,3] Histopathologically, SCAP appears exo-endophytic, often crateriform lesion with a papillary architecture formed by double-layered tubular structures composed of cuboidal to columnar luminal cells, often showing apocrine secretion surrounded by a peripheral layer of basal/myoepithelial cells. Various hyperplastic and metaplastic changes (mucinous metaplasia and squamous metaplasia) and also malignant transformation have been described in SCAP.[4–8] The pathogenesis of SCAP remains unclear, although both in sporadic cases and lesions arising in nevus sebaceus the human papillomavirus (HPV) DNA[2,9] and mutations in the RAS/mitogen-activated protein kinase signaling pathway have been detected.[10,11] The above histopathological and molecular changes have been found in SCAP in its usual location in the head and neck area. Our aim was to study SCAP in the anogenital area and buttock to find out whether the lesions in these sites have different features.

MATERIAL AND METHODS

Case Inclusion/Exclusion

A search in the consultation and routine institutional files of the authors between 1993 and 2017 yielded 243 cases of SCAP, of which 15 lesions involved the anogenital area (penis, mons pubis, vulva, and perianal area) and buttock. One case has recently been seen in routine practice. Hematoxylin–eosin–stained slides were reviewed to confirm the diagnosis, specifically to exclude cases of hidradenoma papilliferum with connection to the epidermis and plasma cell–rich infiltrate imitating SCAP as previously reported.[12–14] The

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TABLE 1. Sequences of *HRAS* Primers

Sequences of *HRAS* Primers (5′ - 3′)	Name of Primer
CACAAGGGAGGCTGCTGAC	*HRAS*-exon 4 reverse
CTGATCCCATCCCTCCTTTC	*HRAS*-exon 4 forward
GGGTCCCTGGCTAGCTGT	*HRAS*-exon 3 reverse
CTCTCGCTTTCCACCTCTCA	*HRAS*-exon 3 forward
CAGCCTCACGGGGTTCAC	*HRAS*-exon 2 reverse
CCCACGGAAGGTCCTGAG	*HRAS*-exon 4 forward
CCTATCCTGGCTGTGTCCTG	*HRAS*-exon 1 reverse
CAGGAGACCCTGTAGGAGGA	*HRAS*-exon 1 forward

histopathological findings were correlated with the clinical data to confirm the location and appropriate clinicopathological context.

Light Microscopic Studies

The number of tissue blocks available for review varied from 1 to 3. The following histopathological features were assessed: exophytic, verrucous and cystic alterations, different types of epithelial cell metaplasia, basal cell hyperplasia, and hyperplasia of luminal cells resulting in a cribriform appearance.

All cases were also examined for the presence of HPV-related features, using the criteria of Meisels for HPV infection (perinuclear halos surrounding hyperchromatic, enlarged angulated nuclei located in the superficial zones of the epidermis). In addition, we looked for granular layer disruption (abrupt alteration in the size, number, form, and density of keratohyaline granules) and percentage of koilocytosis in the spinous layer.[9,15] Any other unusual features, if present, were also recorded.

Twelve cases with available paraffin blocks/unstained slides were studied immunohistochemically for p16 expression (R19-D; Ventana; RTU), using the Ventana Benchmark XT automated stainer (Ventana Medical System Inc, Tucson, AZ), according to the manufacturer's protocol. Diffuse nuclear and cytoplasmic staining was classified as positive p16 staining. No positive cells and weak and focal positivity in some cells were classified as p16-negative staining.

Molecular Genetic Studies

Thirteen lesions were subjected for molecular-genetic studies, including HPV polymerase chain reaction (PCR) and *HRAS* mutations. Twelve cases were analyzed for the presence of the *BRAF V600* mutation.

For molecular-genetic studies, genomic DNA was isolated from formalin-fixed, paraffin-embedded tissue using QIAsymphony DNA Mini Kit (Qiagen, Hilden, Germany) according to manufacturer's protocol on QIAsymphony SP device (Qiagen). Special precautions were taken to prevent HPV DNA microcontamination. The quality of isolated DNA was checked by PCR that amplifies set of control genes.[16]

TABLE 2. Summary of Clinicopathological and Genetic Findings in the Cohort

N	Sex/Age	Location	Histology*	IHC P16	HPV—Types	*HRAS* Whole Gene†/*HRAS* HS‡	*BRAF V600*
1	F/?	Vulva	3, 4, 5, and deposits of mucin in the epithelium	Neg	Neg	Neg/NA	ND
2	F/23	Perianal	2 and 5	Neg	HPV16+	NA/neg	+
3	F/42	Vulva	1, 2, and 5	Neg	Neg (NA)	NA/neg	+
4	F/95	Vulva and labium majus	3, 4, 5, 6, and 7	ND	ND	ND	ND
5	F/81	Vulva and labium majus	1 and foamy macrophages in the stroma	Neg (patchy sq)	Neg (NA)	NA/neg	+
6	F/78	Vulva	7 and 8	Neg	Neg (NA)	NA/neg	+
7	M/60	Perianal	1, 5, and 8	ND	HPV16+	NA/NA	NA
8	F/59	Perianal	5 and desmoplasia	Neg	Neg	c.182A > G, p.Gln61Arg/NA	Neg
9	F/44	Perianal	2 and 7	ND	ND	ND	ND
10	F/65	Right buttock	5 and 9	Neg	Neg	Neg/NA	+
11	M/33	Right buttock	1 and 7	Neg (patchy sq)	Neg	NA/neg	+
12	F/28	Left buttock	3 and 5	Neg	HPV68§	NA/neg	Neg
13	M/18	Buttock	3, 4, 7, and 8	Neg (patchy sq)	Neg (NA)	NA/neg	+
14	F/34	Buttock	1 and 8	ND	ND	ND	ND
15	M/54	Buttock	—	Neg	Neg	Neg/NA	Neg
16	M/79	Buttock	3	Neg	Neg	Neg	+

*1—exophytic; 2—cystic; 3—verrucous; 4—HPV-related morphology; 5—squamous metaplasia; 6—clear cell metaplasia; 7—cribriform structures; 8—basal cell hyperplasia.
†Sequencing analysis whole coding sequence of *HRAS* gene, including exon–intron junction.
‡Codons 12, 13, and 61.
§A very low quality of DNA, we cannot exclude the risk of false negativity for other HPV types.
F, female; M, male; NA, not available; ND, not done; neg (NA), no HPV virus found in the examined sample; however, the quality and quantity of DNA were very low, and therefore, we cannot exclude the risk of false negative finding; patchy sq, patchy staining of the squamous component.

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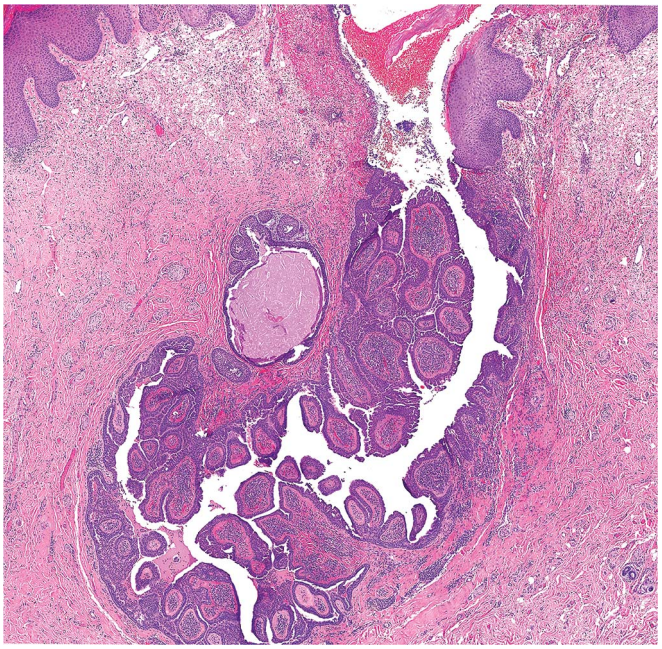

FIGURE 1. SCAP. The tumor has a papillary architecture with a transition from glandular epithelium to the keratinizing squamous epithelium at the skin surface.

The HPV DNA detection was performed using multiple PCR primers from the L1, E1, and E6–E7 regions of the HPV genome as previously described.[17] In brief, primers CPSGB and GP5+/GP6+ targeting the E1 and L1 regions of the HPV genome were used for a wide-range detection of high-risk (HR) and low-risk HPV types, and type-specific PCR detection of E6–E7 region of 6 most prevalent HR-HPV types, namely types 16, 18, 31, 33, 35, and 45, was used to increase sensitivity of HPV detection and to avoid negative finding due to the possible process of HPV integration into the human genome. Furthermore, an RHA kit HPV SPF10-LiPA25, version 1 (Bio-medical Products, Rijswijk, the Netherlands), was run to reveal possible multiple HPV types.

HRAS mutation detection was performed in compliance with the DNA quality of the analyzed DNA. Studied were cases in which more than 300 amplifiable base pairs of DNA were available. The analysis of 4 exons of the *HRAS* gene was performed by PCR using primers listed in Table 1. In cases with a lower DNA quality, only hot spot mutation analysis of exons 2 and 3 of *HRAS* was performed according to the article by Roivainen et al.[18] Amplified products were sequenced on ABI Prism 3130xl (Applied Biosystems, Foster City, CA). DNA sequences were compared with the reference sequence by the online program BLAST.

The analysis of mutations in the *BRAF* gene (codon 600) was performed using the real-time PCR method by commercial kit cobas 4800 *BRAF V600* Mutation Test (Roche, Pleasanton, CA) according to the manufacturer instructions.

RESULTS

Clinical Data

There were 11 women and 5 men, whose ages at the time of diagnosis ranged from 18 to 95 years (median 54 years; mean 52.9 years). In one case, the age of patient remained unknown. In all cases, the lesions were a solitary tumor. Most neoplasms involved the buttock (43.8%) and the vulva (31.3%); less frequent site was the perianal area (25%) (Table 2). No features suggesting nevus sebaceus (linear arrangement and congenital lesions) were mentioned in the patients' charts.

Histopathological Features

All tumors had a papillary architecture with a transition from the glandular epithelium to the keratinizing squamous epithelium at the skin surface (Fig. 1). A dense plasma cell stromal infiltrate presented at the squamocolumnar junction. The glandular component was lined by a luminal layer of epithelial cuboidal to columnar cells surrounded by a layer of basal/myoepithelial cells. Prominent cystic change of the lesion identified in 3 (18.8%) cases. Five lesions (31.3%) were markedly exophytic with an arboreal growth pattern of the glandular elements. Three examples (cases 1, 4, and 13) (18.8%) demonstrated features resembling those seen in warts including acanthosis, papillomatosis, and HPV-associated changes (Figs. 2A, B).

The most common type of epithelial metaplasia was squamous (7 lesions; 43.8%). In one case, there was slight atypia in the squamous epithelium that focally showed rather basaloid cells that along with plentiful mitotic figures occasioned a resemblance to undifferentiated vulvar intraepithelial neoplasia (Figs. 3A, B). One lesion exhibited focal

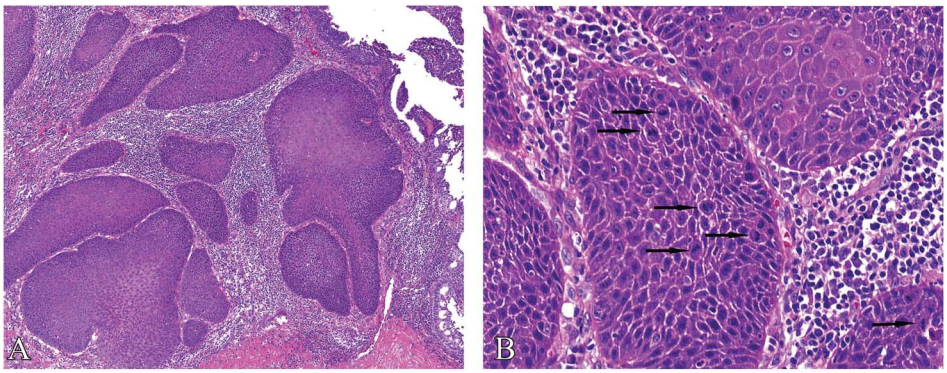

FIGURE 2. Squamous metaplasia with atypia in SCAP (A). Note slight atypia in the squamous epithelium, basaloid cells, and mitotic figures (arrows) (B).

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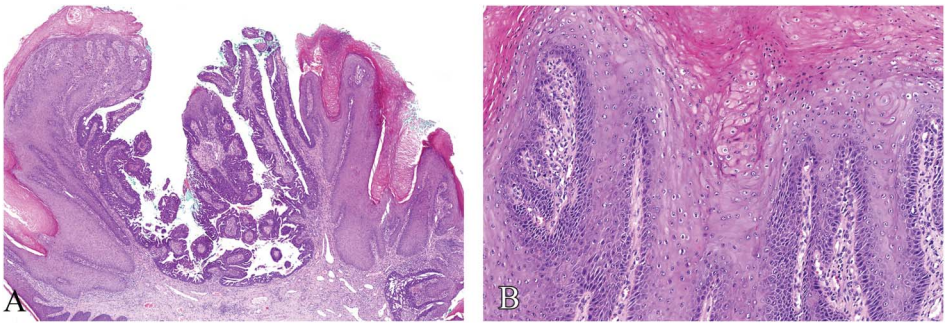

FIGURE 3. Wart-like changes in SCAP, including acanthosis, papillomatosis (A), and HPV-associated changes (B).

clear cell change of the luminal epithelial cells. The hyperplasia of luminal cells, which results in the formation of cribriform structures, was observed in 5 cases (31.3%) (Fig. 4). Four (25%) SCAP showed focal hyperplasia of basal/myoepithelial cells. In one case, mucin deposit was found in the basal part of the squamous epithelium.

Immunohistochemical Data

Among 12 lesions immunohistochemically available for p16 expression, all were scored as p16-negative (3 cases demonstrated a patchy staining of the squamous component) (Table 2).

Molecular Genetic Findings

DNA of HPV HR types was identified by PCR in 3 (23.1%) of the 13 analyzed cases, including HPV16 (2 cases) and HPV68 (1 case) (Table 2).

All but one case were negative for *HRAS* mutations. A missense mutation p.Gln61Arg in the proto-oncogene *HRAS* was identified in 1 lesion (7.7%) (Table 2).

BRAF V600 was detected in 8 of 12 cases (66.7%) (Table 2).

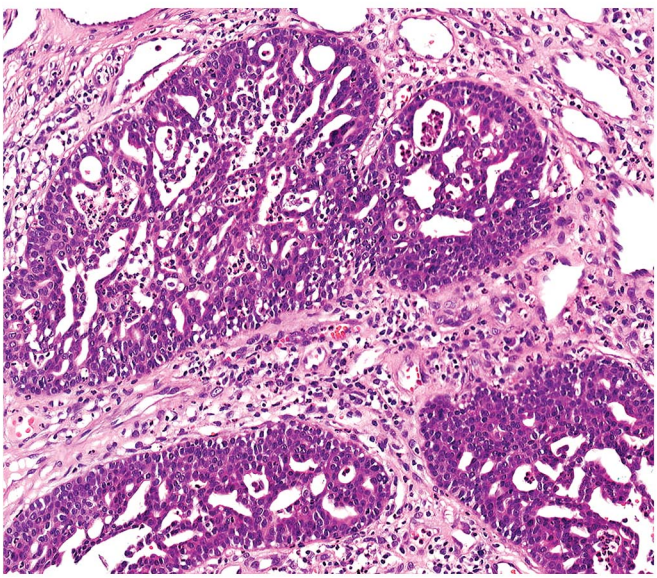

FIGURE 4. Hyperplasia of luminal cells resulting in cribriform appearance.

DISCUSSION

We have described 16 cases of SCAP in the anogenital areas and buttock. Albeit we have not studied a control group of SCAP in its usual location, it seems that there is no significant difference between the morphology of anogenital SCAP and SCAP in other locations. Such histological variations as epithelial metaplasia, cystic alteration, and hyperplastic changes with the formation of cribriform structures have been described in SCAP involved the head and neck, trunk and extremities.[1]

In addition, some SCAP in its usual location and neoplasms affected the anogenital area and buttock have viral wart-like changes presenting as verrucous tumors. Among 18 cases of SCAP with such a morphology described in the literature, the most common location was the cheek (16.7%), scalp (16.7%), and lower extremity (16.7%) followed by the buttock (11.1%), neck (11.1%), vulva (5.5%), sacral area (5.5%), back (5.5%), areola (5.5%), and eyelid (5.5%).[2,19–25]

The cause of such contiguous verrucous proliferations in SCAP is unclear. Some authors have suggested a possible role of HPV infection. Skelton et al[2] reported the presence of HPV 6/11 in the verrucous SCAP of the buttock identified by in situ hybridization. Carlson et al[9] detected HPV 16 type in 1 case and HPV 38 type in a second case of 4 SCAP associated with nevus sebaceus. In our cohort, we failed to identify HPV by p16 immunostaining in all analyzed cases. However, DNA of HPV HR types was identified by PCR in 3 (23.1%) of the 13 analyzed cases, including HPV 16 type (2 cases) and HPV 68 type (1 case). None of these cases demonstrated clear-cut HPV-related cytomorphology (unequivocal koilocytes). However, we noticed features suggesting HPV infection (wart-like acanthosis and papillomatosis) in 3 (18.8%) cases.

BRAF V600E and *HRAS* mutations are most common molecular alterations found in sporadic SCAP.[11,26,27] Shen et al investigated 23 cases of sporadic SCAP with only one case located in the gluteal area. The detection rate of *HRAS* mutations in their study was 26.1% (6 cases), whereas *BRAF V600E* mutations were identified in 52.2% (12 cases), which included a neoplasm located in the gluteal area.[11] Levinsohn et al[27] studied 10 cases of sporadic SCAP and detected *HRAS* pG13R mutations and *BRAF V600E* mutation in 10% and 40% of lesions, respectively.

An immunohistochemical expression of *BRAF V600*E protein has been studied by Friedman et al in 11 cases of

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sporadic SCAP. The positive staining was identified in 7 (63.6%) cases.[25]

The detection rate of *HRAS* mutation in our cohort was 7.7%, which is lower compared with the previously reported material (10%–26.1%), while the frequency of *BRAF* mutations (66.7%) was a little more than the published rates of 40%–63.6%.

In conclusion, we present a series of sporadic SCAP located in the buttock and anogenital area detailing a spectrum of morphological changes that may occur in these lesions. Several tumors demonstrated features resembling those seen in warts, but HPV DNA was not found in these lesions. On the contrary, we identified DNA of HPV HR types in some tumors without HPV-related morphology. Our study confirms the role of *HRAS* and *BRAF V600* mutations in the pathogenesis of SCAP, including SCAP in the anogenital areas and buttock.

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